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CROUCH, D	
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims Now 1-36 are pending in the application.
   Of the above, claims 1-12 and 25-36 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 13-24 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-7 and 10-12, drawn to an oligonucleotide with 2'deoxyribose modifications, classified in Class 536, subclass 27. II. Claim 8, drawn to an oligonucleotide with 2'deoxyribose and phosphate modification, classified in Class 536, subclass 27.
III. Claims 13-24, drawn to a method to modulate production of a protein, classified in Class 435, subclass 69.1.
IV. Claim 9 and 25-36, drawn to a pharmaceutical composition, classified in Class 514, subclass 44.

This application contains claims directed to the following patentably distinct species of the claimed invention: H, OH, halo, azido, amino, thioalkoxyl, haloalkoxyl, alkyl sulfide, alkyl sulfonate, nitrate, nitrite, ammonium, allyloxy, alkeneoxy, or methoxy substitution of the 2'-deoxyfuranosyl and phosphorothioate, methyl phosphonate or phosphate alkylate substitution of the phosphate.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 13 drawn to a modified 2'-deoxyfuranosyl moiety is generic.

Applicant is advised that a response to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. M.P.E.P. § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are distinct because they are capable of separate manufacture. The process for the conversion of a furanoside to a modified furanoside as described by applicant is a separate chemical reaction as to the conversion of a phosphate group to a modified phosphate group as described by applicant.

Inventions I and IV are distinct because they are capable of separate uses. The modified oligonucleotides can be used as probes in hybridization assays, such as Southern analysis.

Inventions II and IV are distinct because they are capable of separate uses. The modified oligonucleotides can be used as probes in hybridization assays, such as Southern analysis.

Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the modified oligonucleotides of invention I can be used as probes in hybridization assays, such as Southern analysis.

Inventions II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the modified oligonucleotides of invention I can be used as probes in hybridization assays, such as Southern analysis.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. John Caldwell on April 25, 1991 a provisional election was made with traverse to prosecute the invention of group III, claims 13-24. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-12 and 25-36 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. A suggested alternative to the title which is more descriptive of the elected invention is "Modulation of Protein Production by Anti-Sense Oligonucleotides Composed of 2'-Halogen Substituted Ribose and Phosphate Modified Nucleotides."

The abstract is objected to as it is not descriptive of the invention. The invention examined pertains to the use of specifically modified oligonucleotides in the modualtion of protein production. The abstract needs to be revised to point out the modifications and their use.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure. Claims 13-24 are drawn to a method for modulating the production of a protein. Although applicant has demonstrated the ability of the oligonucleotides of the instant invention to hybridize in an aqueous solution and the ability to withstand nuclease degradation, applicant has not presented evidence that the

instant invention will be capable of modulating protein production. For this to be enabled the applicant must include details as to the concentration of anti-sense oligonucleotides used and assay conditions. The concentration of oligonucleotides used to modulate protein production is essential as the concentration for effectiveness varies among oligonucleotides. In addition the oligonucleotides are to be used to modulate protein production in an organism. Within a cell the oligonucleotide must be capable of forming a complex with the target nucleic acid in the environment. The high protein concentration of a cell may affect this ability of the anti-sense oligonucleotide. In addition the salt concentration of the cell may also affect hybridization. Additionally, when treating cells or organisms, there is also the question of transport of the oligonucleotide across the cell membrane, and transport through the body in the case of an organism, such as a mammal. With a system subject to such variables, the actual modulation of protein production needs to be supported by data. Applicant has not clearly demonstrated that the anti-sense oligonucleotides of the instant invention at any concentration will under any assay conditions modulate protein production. In particular applicant has not demonstrated the modulation of an HIV protein, a herpes virus protein or a papilloma virus protein. Therefore the skilled artisan would not with a predictable degree of success be able to implement the instant invention without performing an undue amount of experimentation.

Claims 13-24 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 13-24 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are directed toward an organism, but applicant does not specify the type of organism. For example, yeast, bacteria and protozoan are unicellular organisms where as plants and animals are examples of multicellular organisms.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 13-24 are rejected under 35 U.S.C. § 103 as being unpatentable over Ikehara wt. al. (1977) Nucleic Acids Res. 4, 4248-4260 and Marcus-Sekura et. al. (1987) Nucleic Acids Res. 14, 5749-5763. Ikehara teaches that poly(2'-chloro-2'-deoxyadenylic acid), composed at least of 50 nucleotides, and poly (2'-bromo-2'-deoxyadenylic acid) are resistant to nuclease degradation. Marcus-Sekura teaches that the phosphorothioate analogue of an anti-sense oligonucleotide to chloramphenicol transferase (CAT) is about four times more effective than the normal oligonucleotide in inhibiting expression of CAT, when the modified and normal oligonucleotides are transfected into mammalian cells (CV-I). Marcus-Sekura further teaches the that use of anti- sense oligonucleotides which are nuclease resistant would increase stability to the oligonucleotides in the presence of serum and cells both of which contain nucleases. Therefore at the time of the invention it would have been obvious to a person of ordinary skill in the art to prepare anti-sense oligonucleotides containing a 2'ribose halogen substitution, as taught by Ikehara, and a phosphate modification, as taught by Marcus-Sekura, to a DNA sequence to inhibit expression of said DNA as protein, with the added result that so prepared oligonucleotides would be more stable due to enhanced resistance to nuclease degradation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Deborah Crouch whose telephone number is (703) 308-4216.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Dr. D. Crouch
May 3, 1991

Elizabeth C. Weimar

ELIZABETH C. WEIMAR
SUPERVISORY PATENT EXAMINER
ART UNIT 184